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Cross Sectional Comparison of Cytology with Core Needle Biopsy in Suspected Lung Cancer

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A B S T R A C T

Background*:** Lung cancer is one of the most common cancer types worldwide. More than 70% of patients are diagnosed in advanced stages of disease, with options based on cytological and histopathological material.Objectives:***1)To study the cytological features of lung malignancy by Broncho-alveolar lavage (BAL) and Imprint smears; 2) To compare cytological diagnosis with final histopathological diagnosis as gold standard; 3) To assess the sensitivity, specificity and accuracy of cytological diagnosis in detection of lung malignancy.***Methods*:** The present study comprises of bronchoscopic cytology and histopathology of bronchial biopsy in 50 patients suspected of lung malignancies which were obtained between January 2022 to July 2023. Bronchial cytology was evaluated by Papanicolaou society of cytopathology (PSC) system for reporting respiratory cytology**.** ***Results:***The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of bronchial cytology sample was was53.49%, 85.71% , 95.83%, 23.08% and 58.00%.***Conclusions*:** Lung carcinomas are most common worldwide. Analysis of cytology samples provides rapid, safe and inexpensive method of diagnosis.
Keywords: BAL; Biopsy; Cytology; Histopathology; Imprint.

INTRODUCTION

Lung cancer is the term for cancer that originates in the lungs and can go to other organs including the brain or lymph nodes [1]. Lung cancer is the most frequently reported cancer globally, accounting for an estimated 2.2 million new cases and 1.8 million deaths in 2020 [2]. Of the new cancer cases in 2020, lung cancer contributed to 11.4 per cent and 18 per cent of the cancer-related deaths [2]. Smoking is the primary cause, accounting for about 90% of lung cancer cases, with additional risk factors including exposure to asbestos, radon, and certain metals. Passive smoking, radiation exposure, and lung diseases like idiopathic pulmonary fibrosis also contribute to increased risk. Asbestos and radon exposure, particularly in occupational settings, pose significant risks, while residential radon exposure has been linked to a small but notable increase in lung cancer cases, especially among smokers [3].

The pathophysiology of lung cancer is intricate and not fully comprehended. It is believed that repeated exposure to carcinogens like cigarette smoke, triggers dysplasia in the lung epithelium. Continued exposure leads to genetic mutations, disrupting protein synthesis and affecting the cell cycle, ultimately fostering carcinogenesis. Common genetic mutations associated with lung cancer include MYC, BCL2, and p53 for small cell lung cancer (SCLC), and EGFR, KRAS, and p16 for non-small cell lung cancer (NSCLC) [4].

The histopathological classification of lung cancers plays a pivotal role in their diagnosis and treatment. The 2021 World Health Organization (WHO) classification system provides a comprehensive framework for categorizing lung tumors based on their cellular and molecular characteristics. This classification encompasses a range of tumor types including precursor glandular lesions, adenocarcinomas, adenosquamous carcinomas, squamous precursor lesions, squamous cell carcinomas, large cell carcinomas, sarcomatoid carcinomas, lung neuroendocrine neoplasms, salivary

gland-type tumors, neuroendocrine tumors, neuroendocrine carcinomas, and various other epithelial tumors. By identifying and classifying lung cancers according to these distinct subtypes, healthcare professionals can tailor treatment strategies more effectively leading to improved patient outcomes [5].

Respiratory cytology techniques include sputum collection, bronchial suction, bronchial wash, bronchial brush, bronchoalveolar lavage, TBFNA, and TTFNA for studying lower respiratory tract and pleural tumors [6]. Sputum samples are screened for malignancies over several days [7]. Bronchoscopy-based techniques like bronchial wash and brush collect secretions and surface cells [8]. TBFNA and TTFNA obtain cell samples from masses or lymph nodes, with TTFNA common for peripheral lung lesions. FNA and CNB are minimally invasive biopsy techniques, with FNA using a thin needle and CNB a thicker one. Both have advantages, with FNA being less traumatic and CNB offering better tissue preservation [9]. BAL involves flushing and aspirating distal airway samples for diagnosing lung disorders, while touch imprint cytology (TIC) provides rapid, cost-effective diagnosis of tissue lesions by creating imprints on glass slides [10].

To assess the importance of cytology techniques the diagnostic performance evaluation metrics – sensitivity, specificity, positive predictive value (PPV) and Negative predictive value (NPV) are essential to understand the histopathological correlation. Sensitivity measures a test's ability to correctly identify individuals with a condition, while specificity measures its ability to correctly identify individuals without the condition. PPV indicates the proportion of true positives among all positive test results, and NPV indicates the proportion of true negatives among all negative test results. Disease prevalence can affect PPV and NPV. Clinicians should consider these metrics alongside factors like disease prevalence and test complications when interpreting diagnostic test results. Additionally, advancements in autoantibody signatures and imaging techniques like computed tomography (CT) are improving diagnostic accuracy in lung cancer detection, while factors such as biopsy type and patient safety play critical roles in accurate diagnosis [11].

METHODS

The present study comprises of bronchoscopic cytology and histopathology of bronchial biopsy in 50 patients suspected of lung malignancies which were obtained between January 2022 to July 2023.

Bronchial cytology

The Bronchoalveolar lavage (BAL): Fluid is smeared on two glass slides, dried with the help of a hot plate, one is immediately fixed in 95% ethyl alcohol and stained with Papanicolaou stain, the other slide is stained for Leishman and Giemsa.

Imprint cytology: Specimen of bronchial biopsy, before putting in a formalin bottle is put on two glass slides, the imprint of the biopsy is taken on one slide using multiple touch techniques, and fixed with 95% ethyl alcohol and later Papanicolaou staining is performed, the other slide is air dried and LeishmanGiemsa staining performed.

Bronchial cytology was evaluated by the Papanicolaou society of cytopathology (PSC) system for reporting respiratory cytology.

Lung Biopsy

- Lung biopsy was collected in 10% neutral buffered formalin and fixed for a period of 2-12 hours
- Fresh slides were made from paraffin embedded blocks and stained for H & E using standard protocol.
- The sections were stained by routine hematoxylin and eosin

RESULTS

The present study comprises of Bronchial cytology and biopsy specimen of 50 patient received during the period of January 2022 to July 2023. The patients included in this study had suspicious radiological as well as clinical findings of lung cancer with an average age of 62 ± 11yrs (p=0.041).

The 50 cases studied shows similar gender distribution between BAL and Imprint Cytology samples, with around 56% female and 44% male in both groups. No significant difference was noted in gender distribution between the two sample types (p=0.98).

The distribution of malignancy as per cytology results: Out of the total 50 cases, 26 (52.0%) were classified as non-malignant, while 24 (48.0%) were classified as malignant based on cytology.

The distribution of lesion types as per histopthological diagnosis: Among the total 50 cases, 6 (12.0%) were classified as non-malignant, while a majority 44 (88.0%) cases were determined to be malignant based on histopathological diagnosis.

Distribution of diagnosis in BAL and Imprint cytology samples:

In **BAL** (N=16) 56.3% were negative for malignancy, 25.0% positive for malignancy and 18.8% suspicious for malignancy. In **Imprint cytology** (N=34), 50.0% were negative for maliganacy, 44.1% were found positive for maliganancy and 5.9% were found suspicious for malignancy. Later on comparing the suspicious for malignancy to gold standard histopathology diagnosis, it was converted to positive for malignancy. No significant difference in diagnosis distribution between the two sample types was noted (P=0.34).

Correlation of BAL and Imprint cytology diagnosis with histopath diagnosis: Among the BAL group (N=16), 62.5% showed no correlation with histopath diagnosis while 37.5% exhibited correlation. In the Imprint cytology group (N=34), 50.0% showed no correlation with histopath diagnosis and 50.0% exhibited correlation. Overall, 54.0% of samples showed no correlation, and 46.0% exhibited correlation. There was no statistically significant difference in correlation with histopath diagnosis between BAL and Imprint cytology samples (P=0.28).

Table 1: The confusion matrix showing Comparison of Cytology to Histopathology for malignancy detection (BAL)

Diagnostic Criteria		**Histopathology Malignancy**		**Total**
		Negative	**Positive**	
Malignancy as per Cytology (BAL) Negative	Number	2	7	9
	%	True Negative 66.7%	False Negative 53.8%	56.3%
Malignancy as per Cytology (BAL) Positive	Number	1	6	7
	%	False Positive 33.3%	True Positive 46.2 %	43.8%

Cytology correctly identified the absence of malignancy in 66.7% of cases (true negatives), but missed malignancy in 53.8% (false negatives). It incorrectly suggested malignancy in 33.3% (false positives) and accurately detected malignancy in 46.2% (true positives). Overall, cytology's accuracy in detecting malignancy was 56.3%, indicating its utility alongside histopathology but also its limitations.

Diagnostic performance of cytology (BAL) in detecting malignancy compared with histopath diagnosis

The sensitivity of BAL cytology, indicating its ability to accurately identify malignancy, was reported at 46.15% (95% CI: 19.22% to 74.87%), while its specificity, reflecting its capacity to correctly rule out malignancy, stood at 66.67% (95% CI: 9.43% to 99.16%). Furthermore, the positive predictive value (PPV) of BAL cytology, representing the likelihood of true malignancy among individuals with positive results, was 85.71% (95% CI: 52.18% to 97.06%), while the negative predictive value (NPV), denoting the probability of true absence of malignancy among those with negative results, was 22.22% (95% CI: 9.99% to 42.37%). The overall accuracy of BAL cytology in diagnosing malignancy was reported at 50.00% (95% CI: 24.65% to 75.35%).

Table 2: The confusion matrix showing Comparison of Cytology to Histopathology for malignancy detection (Imprint)

		Histopathology Malignancy		
Diagnostic Test		**Negative**	**Positive**	**Total**
Malignancy as per Cytology (Imprint) Negative	Number	4	13	17
	%	True Negative 100%	False Negative 43.3%	50.0%
Malignancy as per Cytology (Imprint) Positive	Number	0	17	17
	%	False Positive 0%	True Positive 56.67%	50.0%

Among cases classified as negative by cytology, all 4 were true negatives, constituting a sensitivity of 56.67%. Conversely, among cases classified as positive by cytology, all 17 were true positives, resulting in a specificity of 100.00%.

Diagnostic performance of cytology (imprint) in detecting malignancy compared with histopath diagnosis

The sensitivity of imprint cytology, indicating its ability to accurately identify malignancy, was reported at 56.67% (95% CI: 37.43% to 74.54%), while its specificity, reflecting its capacity to correctly rule out malignancy, stood at 100.00% (95% CI: 39.76% to 100.00%).

Furthermore, the positive predictive value (PPV) of imprint cytology, representing the likelihood of true malignancy among individuals with positive results, was 100.00% (95% CI: 80.49% to 100.00%), while the negative predictive value (NPV), denoting the probability of true absence of malignancy among those with negative results, was 23.53% (95% CI: 16.97% to 31.66%). The overall accuracy of imprint cytology in diagnosing malignancy was reported at 61.76% (95% CI: 43.56% to 77.83%).

Table 3: The confusion matrix showing Comparison of Cytology (Imprint+BAL) to Histopathology for malignancy detection

Diagnostic criteria			Histopathology malignancy		Total
			Negative	Positive	
Malignancy as per Cytology	Negative	Number	6	20	26
		%	True Negative 85.7%	False Negative 46.5%	52.0%
	Positive	Number	1	23	24
		%	False Positive 14.3%	True Positive 53.5%	48.0%
Total		Number	7	43	50
		%	100.0%	100.0%	100.0%

The confusion matrix compares cytology (imprint + BAL) to histopathology for detecting malignancy. The matrix shows the following results:

- **True Negatives (TN)**: Out of 26 cases where cytology indicated no malignancy, histopathology confirmed no malignancy in 6 cases (85.7%).
- **False Negatives (FN)**: In 20 cases where cytology indicated no malignancy, histopathology revealed malignancy (46.5%).
- **False Positives (FP)**: Among 24 cases where cytology suggested malignancy, histopathology did not confirm malignancy in 1 case (14.3%).
- **True Positives (TP)**: Cytology correctly identified malignancy in 23 out of 24 cases (53.5%).

In total, there were 50 cases, with 7 confirmed as negative and 43 as positive by histopathology (Image 1, 2 & 3). The overall accuracy of cytology in detecting malignancy was 52.0%, with true negatives making up 12% and true positives making up 46% of the total cases.

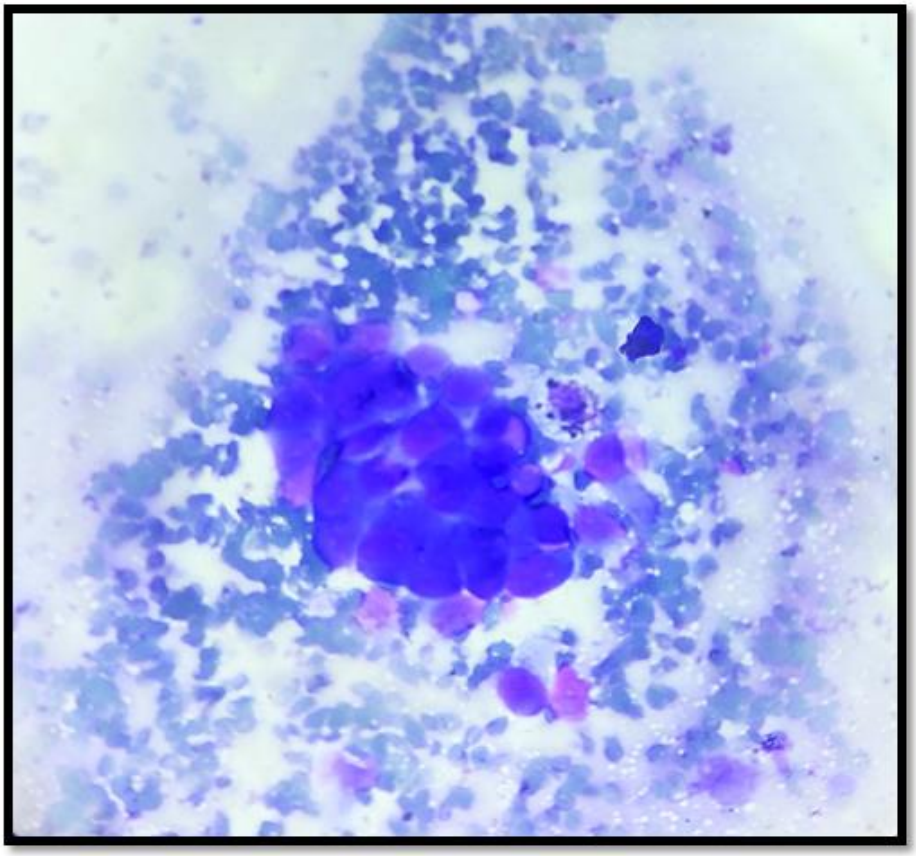

Image 1: 40x view LeishmanGiemsa (cytology): Positive for malignancy

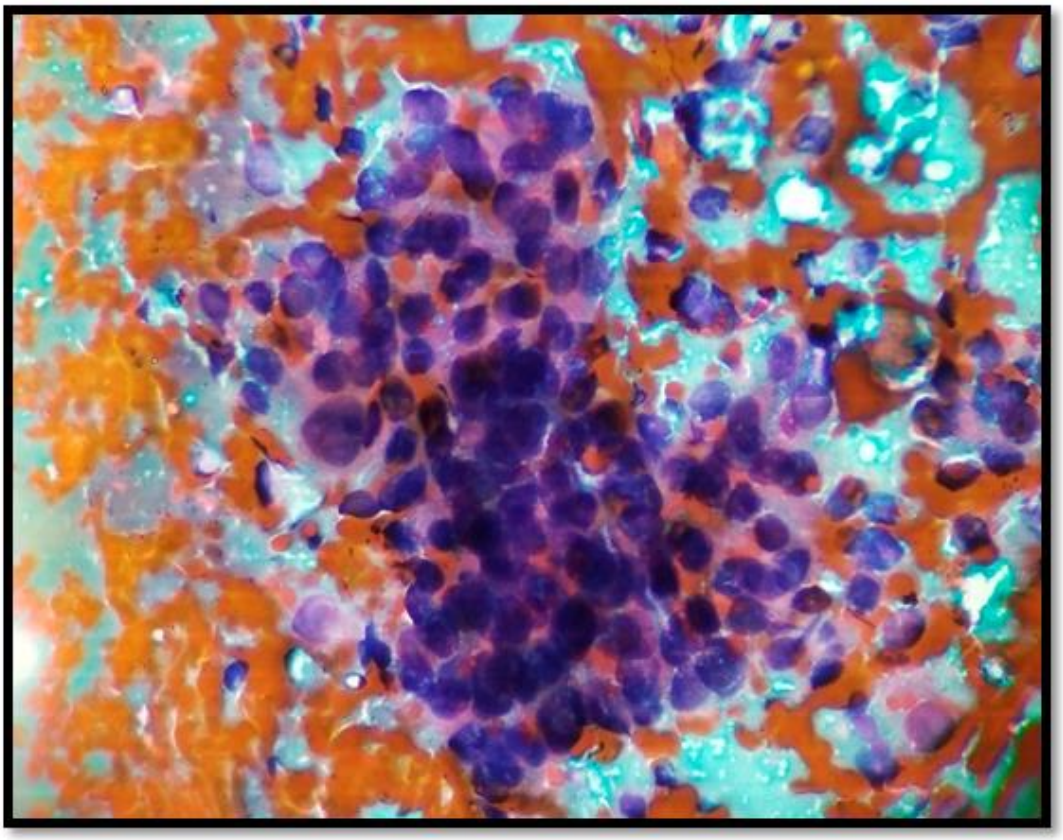

Image 2: 40x view Papaniocolaou stain (Cytology): Positive for malignancy

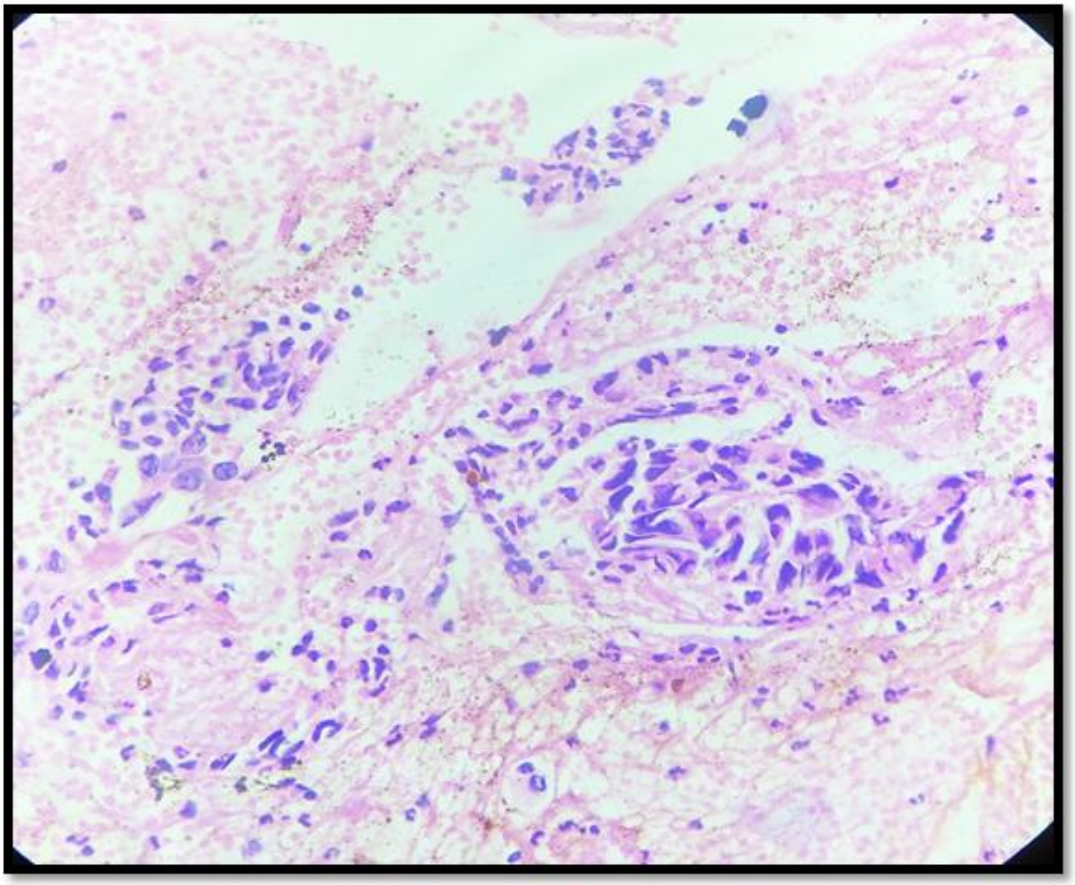

Image 3: 40x view Lung Biopsy (Histopathology): Adenocarcinoma

Diagnostic performance of cytology (imprint+BAL) in detecting malignancy compared with histopathology diagnosis

The sensitivity was 53.49% (95% CI: 37.65% to 68.82%). The specificity, indicating the ability to rule out malignancy, was 85.71% (95% CI: 42.13% to 99.64%).

The positive predictive value (PPV), which reflects the probability that individuals with a positive cytology result truly have the disease, was 95.83% (95% CI: 78.58% to 99.31%). The negative predictive value (NPV), indicating the probability that individuals with a negative test result truly do not have the disease, was 23.08% (95% CI: 16.18% to 31.79%). The overall accuracy of cytology in detecting malignancy was 58.00% (95% CI: 43.21% to 71.81%).

These results suggest that while cytology has a high PPV and reasonable specificity, its sensitivity and NPV are relatively low, indicating that it may miss a significant number of true malignancy cases. The overall accuracy of 58.00% reflects moderate reliability in malignancy detection.

DISCUSSION

Lung cancer was the 2nd most common cancer after breast cancer worldwide, contributing 12.2% of total number of new cases diagnosed in 2020. It was the most common cancer in men worldwide constituting 15.4% and third most common cancer in women constituting 8.8% of all new cancer cases [12].

Bhat N *et al*., studied 902 cases of bronchial biopsy and BAL cytology in diagnosis of lung cancer in India. They obtained a diagnostic accuracy of 42.43% with 78.16% specificity and 35.5% sensitivity. They concluded that although BAL was inferior to biopsy in diagnosing lung malignancies, but was an effective tool for peripheral lung malignancies and when patient was at risk of hemorrhage [13].

Jelena D *et al*., studied the concordance between cytological and histopathological diagnosis of non-small cell lung cancer in 169 cases and concluded that Cytological diagnosis of non-small cell lung cancer is accurate with high sensitivity (94.98%), specificity (98.60%) and benefits for patients [14].

Goel S *et al*., studied 63 lung lesions to compare the cytological and histopathological diagnosis. Their results showed sensitivity of 60%, specifictity of 89%, positive predictive value of 90% and diagnostic accuracy of 71.4% [15].

According to a study by Sareen R *et al*., (2016) CT-guided FNAC demonstrated the highest sensitivity (87.25%) and diagnostic yield (90.38%), followed by bronchial brushings (77.78% sensitivity, 86.67% diagnostic yield) and BAL (72.69% sensitivity, 83.67% diagnostic yield). All techniques exhibited 100% specificity and positive predictive value, with CT-guided FNAC having the lowest false negatives (12.5%) and BAL the highest (27.3%). BAL had the highest negative predictive value (76.95%), followed by bronchial brushings (75.59%) and CT-guided FNAC (70.59%). In conclusion, CT-guided FNAC demonstrated superior diagnostic performance, while BAL remains important for screening lesions, particularly where CT-guided FNAC is not feasible [16].

In the present study the combined results of BAL and imprint cytology concluded the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of bronchial cytology sample was 53.49%, 85.71% , 95.83%, 23.08% and 58.00%, respectively [16].

Our study also revealed 100% specificity in detecting true positive cases with imprint cytology. Only one false positive cases (14.3%) in BAL cytology and it is a relatively safe procedure requiring less expertise, can be undertaken in peripheral lesions and in patients at risk of bleeding. Even those lung tumors which are not visible through bronchoscope might be picked up in bronchoalveolar lavage.

False positive results can primarily arise from the cytologist misinterpreting the smears because of cellular alterations in chronic inflammatory disorders, such as atypical histiocytes in chronic pneumonia, epitheliod cells in tuberculosis, cuboidal alveolar cells misinterpreted as small cell carcinoma in pneumonitis, squamous metaplasia, and alveolar cell polymorphism in lung fibrosis.

The misunderstanding of cuboidal alveolar cells as suspicious or abnormal was the cause of the false positive case in the current study. In questionable circumstances, it is preferable to "under report" rather than "over report," as false positives might have very bad outcomes for the particular patients. Clinical correlation with radiological/bronchoscopic results is required if cytology is positive for malignancy or questionable cells and repeat biopsy is performed.

CONCLUSION

Analysis of bronchial cytology samples provides a rapid, safe and inexpensive method and give additional support to histopathologic examinations.

Hence, use of bronchial cytology in cases of suspected lung cancer is recommended for early and preliminary diagnosis.

Combined use of bronchial cytology and biopsy increases the accuracy and sensitivity of the diagnosis than use the single technique only.

Ethical Considerations: The study was approved by the Institutional Ethics Committee

Data Availability Statement: Data collected solely belongs to department of pathology BVDUMC, Pune.

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Conflicting Interest (If present, give more details): None

Author contributions:

Dr.SurajKumbhar: Primary and corresponding author, Data collection and manuscript preparation
Dr.ReenaBharadwaj: Guide, manuscript preparation, Review and editing
Dr.KundaJagadale: Co-Guide, manuscript preparation
Dr.DivyaTandel: Help in data collectionand analysis

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